Cancer and the Clock: Chronotherapy's Struggle for Legitimacy

by

Emily M. Kagan

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Signature of Author: _____
Graduate Program in Science Writing
June 13, 2004

Certified by: _____
Thomas Levenson
Professor of Writing and Humanistic Studies
Thesis Advisor

Accepted by: _____
Robert Kanigel
Director, Graduate Program in Science Writing
Professor of Science Writing

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ABSTRACT

Circadian rhythms govern almost every process in our bodies. Chronotherapy is the practice of giving medications in synchrony with these rhythms. For cancer chemotherapy, study after study has shown that paying attention timing makes a big difference. Patients receiving chemotherapy at the specified times had their tumors shrink faster and suffered from fewer side effects. In a few studies, patients receiving chemotherapy linked to circadian rhythms survived longer than those who received their drugs at any random time of day. Yet some 25 years after the first human trials, most oncologists still have never heard of chronotherapy. This is the story of why.

From money to attitude problems, logistics to dogma, the tale of chronotherapy's dance around the fringes of oncology has almost nothing to do with the science. Instead it is a story of a promising new therapeutic concept and how it must contend with the interests of drug companies, insurance providers and an overburdened medical system steeped in a culture famously resistant to change.

Thesis Advisor: Thomas Levenson
Title: Professor of Science Writing

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Cancer and the Clock

Ben "Bebba" Woods was a big man--his thick frame offset by a baby face and disarming smile. He was stubborn, strong and accustomed to hard times. Having survived the Holocaust, he was a man who knew pain and he confronted it with a quiet stoicism. Yet even his grandchildren could read the twisted expressions of pain on his face as he battled stomach cancer. He was undergoing chemotherapy, but the toxins that ran through his body were careless assassins, ravaging healthy and cancerous cells alike. They had destroyed his appetite, sense of smell and taste, and left him short of breath. Worse yet, the drugs failed to defeat the cancer.

Across the country in a University of Minnesota research lab, a mouse was undergoing a similar treatment. But this mouse, pumped full of a comparable amount of chemotherapy drugs, was doing far better than Bebba. The mouse suffered from fewer side effects and was able to tolerate even higher doses of the chemotherapy than expected. Most importantly, its tumors were shrinking.

There was nothing particularly special about this mouse. The drugs it was given, 5-FU and leucovorin, were the identical FDA approved drugs that were being administered to human patients at cancer treatment facilities across the country. The drugs were given to the mouse in doses proportional to what a man of Bebba's size would have received, and with the same frequency. The only difference between the treatment that failed Bebba Woods and the one that saved the mouse was the time of day.

Around fifty years ago scientists started noticing that our body's biological rhythms did a whole lot more than govern are sleep-wake cycles. Their research found that internal, biological clocks regulate just about every process that takes place in our bodies. While the part of yourself called "me" performs the temporal gymnastics of waking up, getting to work on time, picking up the kids and cooking dinner, your body cycles on and off a myriad of different processes like metabolism, blood pressure, hormone levels and immune response. With this deepening understanding of biological time-keeping came the idea that these rhythms must affect how the body responds to drugs administered over the course of the day.

Several thousand rats and mice latter, researchers had discovered that drugs did indeed behave differently over a 24-hour span; at certain times they were spectacularly more effective and far fewer toxic side effects. This concept was dubbed chronotherapy (*chrono* from the Latin word for time).

The logic ran from rodents to people. "We know that every cell in the human body has a clock," said oncologist Bill Hrushesky of the University of South Carolina, chronotherapy's leading advocate. "Furthermore, clocks regulate the functions of all the tissues in our boy, including neoplastic (tumor) tissue…" That fact frames chronotherapy's fundamental premise: specifying the time when a drug should be given could have significant impact in the care of human illness -- especially cancer, a disease notorious for its punishing and often ineffective treatments.

Building on the animal studies, oncologists began conducting trials in small groups of between ten and fifty cancer patients. "Now, [the results] are not like 100% percent difference or something," said chronobiology expert Irving Zucker, of the

University of California, Berkeley. “But when you’re life’s at stake, if you can change someone’s probability of surviving 10 more years by 20%, you grab at it,”

Though the trials were small, study after study showed that paying attention timing made a big difference. Chronotherapy doesn’t claim to be a new cure for cancer, yet is does seem to significantly improve the drugs doctors use—and any oncologist will tell you that the drugs currently in use are far from ideal. Patients receiving chemotherapy at the specified times had their tumors shrink faster and suffered from fewer side effects. In a few studies, patients receiving chemotherapy linked to daily rhythms survived longer than those who received their drugs at any random time of day.

Yet some 25 years after the first human trials, most oncologists still have never heard of chronotherapy. This is the story of why.

From money to attitude problems, logistics to dogma, the tale of chronotherapy’s dance around the fringes of oncology has almost nothing to do with the science. Instead it is a story of a promising new therapeutic concept and how it must contend with the interests of drug companies, insurance providers and an overburdened medical system steeped in a culture famously resistant to change.

The Clock

As the alarm goes off, you clutch the blankets closer to your chin and make a small argument against starting the day—the bed is so warm. During the night, your body’s temperature was lowered, causing your sleepy feet to feel cold now as they shuffle towards the bathroom. Your stomach starts to growl as you finish brushing your teeth. The blood flow to your stomach has begun to increase in preparation for

breakfast, but so has the blood flow to your kidneys and your mouth waters while you take your morning whiz. Your joints are stiff as you head down the stairs. Your body's cortisol levels have just started to ramp up for the day, and will soon ease the arthritic attack of your immune system on your joints. It's a sure sign you're getting older. You forgo the butter and eat the toast dry with your scrambled eggs. Your father died of a stroke, so you're trying to keep your cholesterol down. The stroke hit him in the morning, just as his blood pressure was peaking for the day. Now, your doctor has you on heart medication that you take at night. It's a time-release capsule, so that with your morning coffee you're also finally getting the medication from the evening pill. And as you watch the sun streaming through the kitchen window, you start to wake up a bit, the sunlight shutting off the soporific effects of melatonin in your body.

Hundreds of processes in our bodies are constantly turning their volumes up or down, obeying a clock buried deep in our brains. Yearly, monthly and daily cycles can be found in just about every living thing on the planet. It is a consequence of living in a mostly predictable world. We know the sun will rise tomorrow, that the moon will wax and wane with the passing weeks and that a few months after trees regain their leaves, the browns and reds of fall will carry them off once again. With this information, the creatures of this planet can plan to have their offspring born when food is available or arrange to meet at the southern hemisphere, shaded glen or local shopping mall to engage in courting rituals. Evolution has encouraged creatures that can take advantage of the fact that on this planet, things run mostly like clockwork.

While monthly and yearly cycles can be seen in many animals, the most pronounced human rhythms are those that can be seen on a daily basis. Patterns that

repeat around a 24-hour time period are called circadian rhythms, from the Latin "*circa*" meaning *around*, and "*dia*" meaning *day*.

Professor Irving Zucker has spent his career studying our sense of time. He and his fellow chronobiologists have found that animals – including humans -- possess a sophisticated biological clock. Tucked up inside a region of the brain called the suprachiasmic nucleus, or SCN for short, are cells that fire off signals at a regular rhythm, like the steady ticking of a metronome. Zucker has even taken these cells out of the brain, stuck them in a dish and found that they *still* fire with a steady beat. Playing the role of conductor in the biological orchestra the SCN uses hormonal signals to cue different processes to increase their activity or turn it down. Almost every cell in the body has active versions of the genes that respond to the SCN's signals. The SCN is the body's master clock.

While the SCN may get every system in the body ticking at the same tempo, it is our sleep patterns that dictate when the symphony will start and stop. After all, the body needs very different processes to take place when it is awake than when it is asleep. "The SCN provides a representation of day and night cycles in the brain," said Zucker. He also pointed out that no animals exist (except for mutants) with body clocks cycling around something other than a 24 hour time period. Consequently, sleep and wake patterns go a long way toward governing all of our body's other rhythms. When the rhythms are out of sync, health problems crop up. "The evidence of the effects of sleep disorders is indisputable,' said Zucker. For example, when mice have their SCN surgically destroyed their tumors grow two to three times faster than normal. One classic human example of out-of-sync rhythms is a phenomenon called Graveyard Gut.

It takes place in people who do shift work, and find themselves taking a lunch break at four in the morning. At four in the morning, the body should be asleep so the stomach isn't producing much mucus to protect its lining from digestive juices. When a shift worker begins to eat, the gastric juice starts to irritate at stomach lining, producing ulcers, cramps and nausea.

Paying attention to our body's rhythms is as intuitive as taking an antacid tablet before a meal of chili fries, or drinking decaffeinated coffee before bed– and the idea has already been incorporated into the treatment of some common ailments. When the allergists realized that people with asthma often suffered the worst of their attacks during the night, they started to look at ways to deliver the maximum amount of medication to patients when they would need it most—in the middle of the night. In 1989, Purdue Pharma came out with a pill called Uniphyl that, when taken in the early evening, released the maximum amount of medicine hours later, just when asthma attacks were most likely to besiege a person's lungs.

A similarly approach was developed to treat heart disease. Heart attacks are most likely to occur just upon waking. Since people can hardly be expected to take a pill before they wake up in the morning, Searle pharmaceutical company came up with a drug called Covers-HS that was to be taken at bedtime. The drug has a thick coating on it that wears away as the person sleeps, so that the medicine can be released first thing in the morning. It is now standard practice to treat some forms of heart disease in this way.

A second benefit of timing the delivery of medication comes from reducing harmful side effects of a drug. American physicians first saw this principle put into action

it the 1960's. Researchers at the National Institutes of Health showed that people taking a steroid to treat arthritis, asthma and other inflammatory diseases felt better when they took the drug early in the day. The drug, called Medrol, was chemically similar to cortisol, a steroid our bodies produce naturally. Cortisol concentrations in the blood are highest in the morning, and the NIH team found that the drug took advantage of that metabolic pattern: those who took Medrol in the morning suffered from fewer side effects and got better faster than those who took the drug at any old time of day.

These two goals -- increasing efficacy and reducing toxicity, apply across the whole spectrum of medicine. Almost everything doctors do strikes a balance between helping and hurting. In treating a disease like cancer, finding a way to achieve both ends is the central problem of chemotherapy.

The Cancer

The pain in Bebba's stomach eventually got so bad that his doctors sent him in for surgery. The surgeon found a small mass on the lower right side of his intestines, and the biopsy confirmed Bebba and his wife Channa's worst fears: it was cancer.

By any measure, we don't do a very good job of treating this disease. In 1971, President Richard Nixon declared a war against cancer. More than three decades later, according to the American Cancer Society, more than a half million Americans die of cancer each year – more than 1,500 people a day. In 1997, an article in New England Journal of Medicine concluded, "some 35 years of intense effort focused largely on improving [cancer] treatment must be judged a qualified failure."

In large part, that failure stems from the fact that cancer is not the simple, singular enemy implied by President Nixon's call to arms. It can manifest in many

different parts of the body with entirely different profiles. Toxins in the environment, viruses, behavior and random genetic mutation all can cause cancer.

The drugs used to treat the many different cancers are just as diverse. Bebba began receiving two drugs called 5-FU and leucovorin. The goal of these medications was to destroy the cancer cells without killing Bebba's healthy cells. Most chemotherapy drugs try to achieve this end by throwing a monkey wrench in the tumor cell's out-of-control cell division machinery. But both normal and cancerous cells go through this process of replication and division and chemotherapy drugs are indiscriminate killers, unable to tell the cancer apart from normal, healthy cells. That shotgun approach produces the horrible side effects of taking cancer-killing compounds—nausea, diarrhea, hair loss, mouth sores, and low white blood cell counts known as leucopenia, to name a few. For many people, their bodies become too ransacked by the drugs to allow them to finish their treatment As radiologist Tyvin Rich of the University of Virginia pointed out, "It's a two-sided coin: kill the cancer without killing the patient."

Bebba seemed fortunate. He tolerated the side effects better than most. Though he lost his appetite, sense of taste and smell and had none of his usually energy, he was able to finish the full course of chemotherapy. After finishing his chemotherapy, the doctors snaked a scope down into his stomach to look for the cancer. It had vanished. Bebba's cancer had been visibly eradicated by the chemotherapy. But then, just four months later, it was back.

In most diseases, treatment is considered successful only if the patient is cured. But measuring five-, eight-, and fifteen-year survival rates only gives an incomplete picture of treatment success for cancer, as most patients never live to reach those

milestones. This places doctors in a difficult position: How can they gauge improvements if most of their patients ultimately succumb to their cancers? While they always hope to meet the gold standard of cure, oncologists have become more pragmatic; they have come to measure the success of a treatment based on more attainable, secondary goals.

Perhaps the most important secondary measure is tumor response rate—whether the tumor, or evidence of the tumor, has been reduced by at least 50 percent, and does not regrow for at least three months. For example, if a new drug study reports a 35 percent tumor response rate, it means that 35 percent of the people in that trial saw their tumors shrink by at least 50 percent or more. On this scale, Bebba' treatment worked: the tumor responded to the chemotherapy, even though it later came back.

This measure can be seen as a success because simply shrinking the tumor's size can go a long way towards improving the quality of life for the patient. In the best of cases, shrinking a tumor means that it can then be surgically removed, dramatically improving a patient's chance for survival. At a minimum, reducing the tumor's size can relieve a patient's pain. Tumors are painful because as they grow they push up against adjacent nerves. Shrinking the tumor will ease the pressure on the nerves, even if the cancer never fully disappears. This is the kind of benefit that oncologists are talking about when they use the phrase "quality of life.

What quality of life truly means varies from patient to patient. For some, it means being able to live free of pain. For Bebba it meant enduring as much toxicity as possible to buy just a few more days with his family. The National Cancer Institute defines the term as "the overall enjoyment of life." More and more frequently clinical trials are

required to measure the impact of treatment on a patient sense of well-being and ability to carry on their normal lives. When a treatment claims to improve quality of life, it is because patients are reporting fewer incidents of side effects, and the problems they do experience are less severe. While these measurements are based on patient self-reports, they are converted into numbers using standardized scales established by the World Health Organization. For instance, during Bebba's last days, he had become anorexic from the intense nausea. The World Health Organization would call this grade four nausea, meaning that it required hospitalization.

Since many patients will die of their cancer, the quality of the time they do have is extremely important – and current cancer treatments are among the most odious in medicine. That's why researchers like Georg Bjarnason of Toronto-Sunnybrook Regional Cancer Center see chronotherapy a natural fit, "it has the potential to improve the therapeutic index, meaning it can improve the activity and reduce the toxicity." Chronotherapy for cancer treatment makes good sense. But good sense can also tell you that the world is flat. What oncologists need is evidence.

From Mice to Men

Starting in the 1950's, oncologist Franz Halberg at the University of Minnesota began doing cancer chronotherapy studies on animals. By implanting human tumors into mice and rats Halberg was able to test for the best times to give different cancer drugs. Between 1977 and 1996 researchers, most of them trained at Halberg's lab, used rodents determined the best tolerated time for twelve common anti-cancer therapies (including 5-FU and leucovorin). During those 19 years, the studies showed

that timing could significantly change the effects of anti-cancer drugs, making them between 25 and 600 percent for effective at shrinking the tumors. Coincidentally, the time of day that the rodents saw their cancers shrink the fastest was also the time of day at which the chemotherapy had the fewest side effects.

But this research was no guarantee that the results could be duplicated in humans. Walk into a mouse room in a chronobiology lab and you are struck by more than the smell of sawdust and urine. The lab mice live in identical plastic boxes with running wheels attaches to data-collecting wires. On the walls you see urgent looking notes bearing the rather mundane reminder to not mess with the light switches. The mice are on a tightly regulated light/dark cycle. To even reach the mouse rooms you have to pass though a darkened anteroom, so that not even the smallest bit of unwanted light can seep in under a beveling doorframe. The conditions that humans live in are far more variable. So there was some question as to whether humans and rodents even had comparable rhythms, especially since rats and mice are nocturnal animals. Despite their uncertainties, researchers felt that the potential benefits were great enough to justify the next step: clinical trials in human cancer patients

Beginning in the mid 1980's a few doctors started administering chemotherapy at the times that the animal studies suggested that the drugs would be best tolerated. The studies were small, ranging from 20 to 100 patients, but through trial after trial, a picture emerged of chronotherapy's ability to improve cancer treatment. It was working.

In one of chronotherapy's most frequently touted studies, 186 patients with colon cancer were followed at nine hospitals throughout France, Italy and Belgium. Patients were randomly assigned to receive their medication at a constant-rate or on a

continuous basis, with a peak at the optimal chronotheraputic time. The patients receiving constant-rate infusions, the standard of care, had a tumor response rate of 29 percent, which is to say that 29 percent of patients saw their tumors shrink to half their size and stay that way for at least three months. Those who received their drugs on a chronotheraputic schedule had a tumor response rate of 51 percent. Not only were their tumors being treated more effectively, patients who received chronotherapy were also one-fifth as likely to experience the side effect of severe mouth sores, and they were half as likely to experience peripheral neuropathy, a form of nerve damage to the hands and feet. In 1997 these results were published in the British medical journal *The Lancet*.

This study "confirms the clinical relevance of chronotherapy and call[s] for its integration into the early stages of anticancer drug development," said lead researcher Francis Levi of the Paul Brousse Hospital in France. Since then, clinical trials for colorectal cancer have involved up to 2,000 patients. A 2002 assessment of these trials by the authors reaffirmed their findings. There was one important caveat: despite the gains in quality of life, the 2002 paper reported that the new approach did not show that long-term survival rates were improved. Five years later the same number of people had died from their cancer, regardless of the method of treatment.

Other trials, however, have linked chronotherapy to improved survival rates. A Canadian study done in 1985 showed that children who were being treated for acute lymphoblastic leukemia (ALL) did have improved long term survival when treated in the evening instead of the morning. Of the 118 children, the 36 who were given their medication in the evening were more than 4 times as likely to be alive after eight years. They were more than twice as likely to be alive and disease free after 15 years. There

were some issues with the statistical methods used to choose the two groups in this study, but the results were robust enough to be published in a 1993 article in *The Lancet.*

Other studies have shown similar results. Researchers at South Carolina's Veteran's hospital found that ovarian cancer patients also had improved survival rates when their medications were given at the optimal time of day. When the team noticed that giving the drug doxorubicin in the evening made it difficult for white blood cell counts to recover to normal after treatment, they decided to try administering the drug in the morning. When they randomly assigned this schedule to 37 ovarian cancer patients, giving doxorubicin in the morning and giving another drug called cisplatin in the evening, 44 percent of patients were alive after 5 years. When these drugs were reversed, only 11 percent of patients survived to the five-year mark. The results were published in the journal *Science*.

These trials involved drugs that are already being used to treat patients. They were given at doses and frequencies that are FDA approved. The only thing that was changed was the time of day at which drugs were given. In no case to date has chronotherapy been shown to be less effective than standard scheduling. At the very least, in patients tested so far, giving chemotherapy at the times of day when it is best tolerated shrinks the tumors more effectively and reduces the number of side effects. These studies have been published in peer reviewed, highly respected medical journals including *Nature*, *The Lancet*, *Cancer*, the *Journal of Clinical Oncology*, *Cell*, the *Journal of the National Cancer Institute*, *Science* and the *American Journal of Pathology*. Both the American Cancer Society and the FDA have information about chronotherapy

available on their websites. Feature articles have been written about this subject for the *New York Times*, and a segment on NPR's Science Friday was devoted to this topic.

Yet 25 years after the first promising results were published, not only most patients, but most oncologists still have never heard of chronotherapy.

The Business of Medicine

A good way to start finding the source of any problem is to follow the money. Pharmaceutical companies, the major financial backers of clinical cancer research, need to be able to sell a product and turn a profit. The investment in bringing a new drug or therapy to market is considerable. Beverly Teicher, Vice President of Oncology research at the Genzyme pharmaceutical corporation outlined how the costs add up.

Once a drug looks promising in the lab, it must be manufactured in larger amounts to use in human trials. The first trials in humans, called phase I and II trials, are usually limited to 20-100 people total, but many drugs fail in these early trials. Regardless, the FDA requires that the pharmaceutical company build the drug's manufacturing plant before the human trials are completed. Assuming the drug passes these first two trials, and the manufacturing plant has been built, the drug moves on to a phase III trial.

For doctors, this is the ultimate test for any new drug or therapy. Though it is officially called a randomized, controlled phase III trial, this is just a fancy way of saying that patients are randomly selected to be followed in (at least) two groups, one receiving the experimental therapy and one treated in the standard way. Doctors want to see that

at the end of the day, when the groups are compared, the new treatment surpasses the old—and they want to see this result in thousands of people. Consequently, large-scale phase three trials are multi-million dollar endeavors. A recent study by Tufts University estimates that the average cost of bringing a new drug through all stages of testing and on to the market is about $800 million.

Chronotherapy offers nothing for a drug company to sell. At best, it improves the drugs that are already on the market, those upon which oncologists already depend. If pharmaceutical companies can get these drugs FDA approved under current standards, they have no obvious financial incentive to improve a drug's efficacy by specifying a time of day. Regardless of how interesting the science may be, the bottom line is the bottom line. As Los Angeles oncologist Avrum Blumming noted, most of science today is driven by what he calls enlightened self-interest. "Enlightened self interest means that if you're Merck or Pfizer or Bristol-Meyers Squib you'll pay for studies because it might help you and it might also help the world. But you won't pay for studies if its not going to turn around to help you, even if it's going to help mankind."

To round out the pharmaceutical companies' list of strikes against chronotherapy, add liability issues. When I asked oncologist Eric Nadler of the Dana-Farber Cancer Center, and professor at Harvard's Medical School why the trials are so difficult to implement if changing the timing of a drug would at least do no harm to the subjects, he countered, "But it can. What if it's given at the wrong time?" It is possible that these studies will not only show that chronotherapy is better than traditional means of drug delivery, but that giving medications at any random time of day may in fact be harmful to the patient.

Hrushesky adds to this concern by pointing out that sometimes the same compound can have opposite effects at different times of day. Take interlukin-2 for example, a compound that is commercially available. Hrushesky's team has shown that when given at certain times it can control cancer growth. When given at other times, Hrushesky said, "It's Miracle Gro for cancer".

If what Nadler and Hrushesky say is true, chronotherapy may be a huge liability risk. MIT researcher Robert Langer knows how difficult it is to get the pharmaceutical industry to invest in novel ideas when a potential liability issue looms. Langer gained valuable experience serving on the board of Wyeth pharmaceutical company—makers of the weight loss drug Fen-Phen. Fen-Phen was pulled off the market after it was linked to several deaths. The debacle resulted in $21 billion in lawsuits for Wyeth. Langer worries that years of expensive and sometimes ruinous litigation have made many companies wary of backing new ideas. Having also worked with Bill Hrushesky, Langer understands the importance of timing medications. Pharmaceutical companies may be looking at the implications of chronotherapy, wondering who could be liable for having delivered drugs at the wrong times.

But for all the reasons drug companies may resist funding chronotherapy, proponents say that strong arguments can be made for pursuing it—not the least of which are increased profits. Proponents say that pharmaceutical companies could use the principles of chronotherapy to find more anti-cancer agents. According to Malcolm MacCross, vice president of basic chemistry and drug discovery at Merck pharmaceuticals, only about one out of every 300,000 compounds that a drug company looks into ends up making it to market as an FDA approved drug. Chronotherapy

researchers believe that some of these drugs are failing because they are being tested at the wrong times of day.

Bill Hrushesky cited an example from his own research. Tumor necrosis factor (TNF) has been studied as an anti cancer agent, but it causes severe side effects. Hrushesky's team confirmed TNF's toxicity, but they demonstrated that the drug's side effects became ten times more dangerous over the course of the day. The also showed TNF's ability to control cancer varied throughout the day. Hrushesky argues that if TNF were given at the right time of day, it would be less toxic and would be much more effective at killing the cancer cells. TNF is still not approved for cancer treatment. "It's been removed from the therapeutic pipeline." Hrushesky said, with an edge of frustration creeping into his voice. "TNF was thrown away because it was too toxic." If the pharmaceutical companies took circadian timing into consideration they might well see changes in the efficacy of their compounds and a higher percentage of drugs would make it to market

Chronotherapy's proponents also argue that conducting the trails necessary to make chronotherapy a standard part of oncology will be far less expensive than estimated. The drugs to be used are already developed, FDA approved and on the market. The manufacturing plants have already been built and many of the phase I and II trials have already been conducted by small groups of dedicated researchers. Franz Halberg, one of the forefathers of chronotherapy, argues that paying attention to the time when drug are delivered could actually reduce the number of people needed as subjects in phase III trials, saving drug companies several million more dollars. The reason phase III trials need to be so large is that there is a tremendous amount of

variability in how each person will react to a new drug. Sample only 20 patients, and you might see no clear result. Sample 2,000 and a pattern will emerge. Halberg argues that part of the reason so much variability exists is because the drugs are administered at random times of day. By his logic, if the researchers stipulate a time at which the drug should be administered, it will cut down on the variability between the patients and a statistically meaningful result will emerge with even fewer people studied.

Some feel that human chronotherapy studies can even be done without drug company funding. Oncologist Avrum Blumming suggests that doctors can collect information about the timing of drugs in their own practices. "If what you're doing is using standard treatments such as chemotherapy and all you're doing is altering scheduling, then the only thing you really need money for is data collection," he said. "So you get File Maker Pro and you collect data." But Blumming knows he is being idealistic. Most oncologists barely have enough time to see all of their patients, let alone collect, analyze, and write up study results.

There's a more pressing objection to Blumming's pipe-dream. Even if they had time and funding could be found, oncologists might still ignore chronotherapy.

The Sociology of Medicine: Martyrs and Capacity for Obsession

Los Angeles oncologist Raul Mena drips raisins onto his bowl of oatmeal as he speaks "Do I think there's something to it?" he says, taking a spoonful into his mouth. We have met for breakfast to discuss his views on chronotherapy. "I think there's something to it." He folds his hands across his chest, leans back and closes his eyes—a habit he has when he is about to make a point. "I just don't know if it is clinically

significant. And the only way we're going to know that is with a big randomized phase III study." This was a sentiment echoed by every single oncologist interviewed for this article—they'd be willing to consider chronotherapy if they knew of enough evidence to support it.

The colorectal cancer study was a big, randomized phase III trial, but in the nearly 10 years since it was published it has yet to reshape the way doctors treat colorectal cancer. So what is "enough" evidence? It's hard to get a straight answer.

Oncologist Robert Mayer, a dean at the Harvard Medical School, said that there would be only three reasons to pursue chronotherapy: first would be for better outcomes, second would be decreased toxicity and third would be if chronotherapy proved to be cheaper, more convenient or improved quality of life. But how much better would the outcomes have to be? By how much would the toxicities have to decrease? One way to tie these broad terms to more concrete numerical values is to use the same standard of evaluation that drug companies use in assessing new products. When Beverly Teicher's evaluates the evidence for a new Genzyme drug, she uses a rule of thumb: to pass phase II clinical trials, she wants to see a 20 percent increase in tumor response rate, to pass phase III, she only needs to see at least a 15 percent improvement over the standard of care. As it happens, one can find more than a dozen papers on phase II trials that meet the standard. The phase III colorectal cancer trials showed a 21 percent improvement over the current standard of care. Using Mayer's and Teicher's criteria chronotherapy should be well on the way towards becoming a regular part of cancer treatment.

Perhaps the problem isn't a matter of getting enough evidence, but a matter of from where the evidence comes. As Mayer critiques chronotherapy, he pulls large blue volumes off the shelf in his office, piling them high onto an already overflowing desk. Printed on the spine in big white letters are the words American Society of Clinical Oncologists (ASCO). Each volume contains a record of the cancer clinical studies conducted in a single year and submitted for presentation at the ASCO annual meeting. As he flips through the index for the term "chronotherapy," he consistently comes up short. He finds only three papers on the subject in ten years of reports. After thumbing though the 2004 book, he sits back down at his desk and shakes his head at me. No one in the United States finds chronotherapy significant enough to investigate, he concludes.

But the 1997 colorectal cancer trial wasn't conducted in the United States. It took place in France. Its results were published in the British medical journal, The Lancet. Do a medical journal search for the terms "chronotherapy" and "chronopharmacology" and you'll find that 30 percent of the research articles are not in English. This creates a huge information gap for American doctors, because most of them don't read cancer journals from other countries.

Sociologists have long commented on the different ways that medicine is practiced in countries around the world. This has led many doctors and researchers to make claims and assumptions about the quality of foreign research. Speaking of American attitudes, "They think these studies have been conducted poorly," said Francis Levi, head of the European Organization for Research and Treatment of Cancer

and the principle investigator on the phase III colorectal cancer study. "Sometimes this is the case for U.S. studies!"

But *The Lancet* is an internationally well-respected journal, well known and read in the U.S., and many chronotherapy trials have also been published in the leading American clinical cancer journals. Anyone with an internet connection can log on to the National Library of Medicine's web site and search for these articles, including their English translations.

So international name-calling may not be the entirety of the problem. Part pf the problem lies with the sheer volume of noise that confronts the working clinician. In 1997, the year that Levi published his colorectal cancer study, 3,414 other articles were published relating to colorectal cancer alone. It's easy to see how some findings can be overlooked.

Still others argue that the opposition to chronotherapy is driven by something more complicated by simple ignorance. South Carolina's Hrushesky contends that the idea behind chronotherapy directly threatens one of the central pillars of physicians' self image: their role as care-givers, bringing succor to their patients. "We can talk about practicalities, and that it is difficult to apply, but I don't believe that is really the reason why [chronotherapy] hasn't been applied. I believe the reason this hasn't been applied is because it is a foundational idea. There aren't that many foundational ideas in medicine." He points to the case of Ignaz Semmelweis, one of the founders of germ theory. Over one hundred years later, we take the notion of hygiene for granted. But around the turn of the last century, doctors were extremely resistant to the idea that they might be transmitting infections to their patients because they hadn't washed their

hands. The notion that the doctors themselves may be causing harm ran counter to their whole sense of purpose.

Because of the nature of their job, oncologists are a particularly difficult subgroup of doctors to confront. The field attracts many of the brightest minds in medicine and commands vast sums of research dollars. Yet oncologists must confront the blunt fact that for all their effort, most patients die under their care. In a 1997 New England Journal of Medicine article, the authors acknowledged that there has been significant progress in treating children and young adults with cancer, better management and understanding of cancer, and better palliative care for advanced cancer. But overall the authors still felt that "though these benefits must not be discounted, their effects on mortality due to cancer have been largely disappointing."

With reviews like that, an oncologist must have some capacity for obsession to work in this field. They must believe that even if the majority of their patients succumb to their cancer, seeking medical attention can by them some time. An oncologist's relentless willingness to confront an enemy with obviously deficient weaponry can take its toll. "The people who practice medicine take a tremendous amount of responsibility onto themselves," says Hrushesky. "And if they're dealing with a disease that has naturally poor outcomes, they're under tremendous stress and strain as it is. When they are giving drugs that cause people to be sick and sometimes even to die, those responsibilities are very heavy. And then to be told that you are inadvertently harming people because you're not paying attention to principles that are fundamentally new..." Hrushesky's voice trailed off as he contemplated this last point. "And people are doing

harm," he said, coming reluctantly to his own conclusion. "They are actively doing harm by ignoring stuff that's been in the general medical literature for 30 years."

Hrushesky's comment brings up another factor in the world of oncology: the difference between researchers and clinicians. Researchers familiarize themselves with the intimacies of cancer biology. Clinicians, or oncologists, are the ones who treat patients. The two tasks give each a unique perspective on the problem. Researchers can take a gamble on new ideas because their work mostly takes place on a molecular level. As Hrushesky noted, "Science can still make fun of you, but if you can get your ideas into a format that makes sense to your colleagues, they'll give you a shot." The risk to a lab trying out a new therapy is the loss of a couple of lab mice.

For physicians the stakes are much higher. Clinicians tend to be more cautious about new ideas – especially in the cancer field. And to a large extent, they have to be. They know that patients with a terminal disease will jump at any new therapy if they think it can save their life. "If you have a patient with terminal disease, they'll take glue or Drano if you give it to them," said Nadler. Patients look to their doctor to make well-reasoned decisions about the benefits of any experimental treatment. It is important that oncologists not gamble with their patients' lives because of one interesting study in the New England Journal of Medicine. Hrushesky is quick to agree, "You don't want to have medicine change with every breeze that blows." But this resistance can manifest itself as stubbornness. American doctors have reputations for being hard to convince on many subjects. They require a great deal of scientific evidence, and then some, before they change their practices. This stubbornness, coupled with an inherent resistance to

ideas that challenge medical dogmas can help protect patients, but it can also prevent good ideas from breaking through.

But some researchers feel that the work is being overlooked because of another human shortcoming—the capacity for one brilliant person to make himself insufferable.

The Crusader

Bill Hrushesky is a stocky man in his 50's, with a thick head of grey hair and a nervous habit of twisting the ends of his mustache. Yet his most obvious feature is his passion. He signs e-mails to colleagues "love, Bill." He gives hugs when parting company. He is the most enthusiastic fan at his daughter's soccer games. But some of his passion, at least that which surrounds his work, seems to come from years of presumed martyrdom. "Now, in my 30 years of medical practice I have been criticized and I have been attacked as doing unorthodox things, simply for applying the principles that I have published in places like *Science*." Hrushesky says, with a rising air of frustration. He likens himself to Semmelweis, the 19th century doctor who first suggested that medical students might be transmitting diseases to their patients by not washing their hands. Semmelweis was fired for publishing his results, committed to an insane asylum and eventually killed himself. Today, the university in Hungary where he worked is named for him. "I have definitely had some Semmelweis-ian experiences in my life," Hrushesky said. They have made him defensive and impatient.

Hrushesky is arguably chronotherapy's biggest champion. He was introduced to the subject in 1976 while working at the NIH as part of a medical training program he signed up for to avoid being drafted into the Vietnam War. Some colleagues had

showed him a paper by Franz Halberg detailing the various effects of a cancer drug called Ara-C. Halberg had given mice Ara-C at several different times of day and found that a lethal does at one time was actually well tolerated when given 3 hours later. Hrushesky himself was doing research on high-dose chemotherapy and was intrigued. He applied for a teaching position at the University of Minnesota medical school and went to track down Halberg.

Halberg is a workaholic. So when a new professor called and asked to speak with him about chronobiology, he said that he had some free time at 4:30—in the morning. Hrushesky, being a more practical man insisted on an earlier time. Fine, Halberg said. Come by at 3am. Hrushesky bundled himself up, but at 30 degrees below zero no amount of layers would keep out the February night air. He made it to Halberg's place and the two men began to talk. They didn't stop until 3 in the afternoon.

"I took away three things from that conversation." Hrushesky recalls. First, he concluded that Halberg was on to something. Second, if Halberg was right, his ideas about coordinating medication to circadian rhythms would be foundationally important to all of medicine. Third, and perhaps most importantly, Hrushesky decided that he had found his calling.

"It was so obvious and so anti-paradigmatic that being a physician, and knowing physicians, I just knew this field would be ignored unless I spent some number of decades or years determining whether it was relevant to humans." So Hrushesky set out to work in Halberg's lab, eventually coming to lead his own team in chronobiological research. The Hrushesky lab turned out some important alumni. Francis Levi, the leading chronotherapy researcher in Europe, did his training at this Minnesota lab.

Having put together an alliance of several world research institutions, Levi has been able to conduct some of the largest clinical trials in the field of cancer chronotherapy. "Francis is a diplomat," Hrushesky says. "He has the tolerance to build a coalition." Hrushesky admires Levi's work, especially because he knows he couldn't do it himself. "How many times can you explain the same damn thing?" Hrushesky lamented. "I don't have the patience to be a politician."

Patricia Wood is another important alum. Having earned both an MD and PhD, Wood gave Hrushesky the perspective of a basic researcher. She co-authored numerous articles with Hrushesky, designed animal trials to elucidate critical aspects of circadian biology and soon began running the lab. But political fallout forced Wood and Hrushesky to leave the University of Minnesota to eventually settle down in South Carolina. Formally, they left because there was tension between the hematology department where Wood had trained and the oncology department where she wanted to transfer. But with a wry smile Hrushesky admits that a big reason they left was because his tenure had been delayed—on account of his marrying Dr. Wood.

Hrushesky slips easily between an erudite description of his latest paper and four-letter admonishments of those who don't seem to get it. It is a fine spring afternoon in Columbia, South Carolina and Hrushesky speeds the green BWM through town. With the top down the warm air should whip anyone's face into a smile, but not Hrushesky. He's angry. We've just gone to hear Nobel laureate Joseph Goldstein give a talk about metabolism on the University of South Carolina campus. When Hrushesky stood up and asked Goldstein a question about circadian timing of metabolism, Goldstein had little to offer. Hrushesky didn't get to ask a follow up question. He was indignant. How could

Goldstein ignore something as fundamental as timing?! As we pull up to the lab on the university's medical campus, Hrushesky is thinking aloud. "It's good that we went to hear him. I understand now how he thinks. It's linear." Hrushesky, on the other hand, believes himself to be a non-linear thinker—one who has the gumption to investigate big, messy problems like chronobiology. "Personality has a whole lot to do with discovery," he mused.

Those who know Hrushesky's research find it fascinating. But ask someone about the man himself and you are met with rolled eyeballs and requests to speak off the record. Hrushesky is a bad man to challenge. He is easily frustrated with people who don't understand his points, often choosing simply to repeat himself more loudly as an attempt at clarification. He has the unnerving habit of posing a question and then insisting that you squirm for the answer he has already deduced for himself. One night at dinner he ended a discussion by shouting down his closest ally, his wife. Several times during my visit I watched Dr. Wood temper his anger and measure his response, prompting me to think about what lies behind every great man.

Especially in science, a field that prides itself on its presumed impartiality, passion like Hrushesky's can serve to discredit a researcher. Such scientific zealots are thought to have too much invested in the work to pull off good research. But by all outside measures, Hrushesky does good research. He has published in many of the most highly regarded scientific journals including *Cancer*, *Science*, *The Journal of Clinical Oncology*, *The Journal of the National Cancer Institute, The Lancet* and *The American Journal of Pathology*. "He's a visionary guy," says MIT's Bob Langer, who has worked with Hrusheky. "But visionary work is hard."

When an idea is working its way into the mainstream, can it afford to have such a contentious leading advocate? Both the National Institute of Health and the Veterans Administration have funded Hrushesky's work, so his personality hasn't affected his ability to pay for his research. Teicher, who has served on several granting committees, thinks that personality shouldn't matter, especially when so many oncologists have such strong, dominant and egotistical personalities. But Blumming has seen people respond to Hrushesky first hand. "When he starts to talk with such messianic fervor, people just turn him off. Part of the reason [chronotherapy] keeps dancing around the fringes of medical oncology is because Bill becomes abstruse."

Hrushesky does get calls from physicians, even if they aren't incorporating his study results into their practices. "Physicians, often call me. But do you know when they call me? When it's their wife, or their mother who's sick."

Logistics and Technology: Will it play in Poughkeepsie?

But assume that funding can be found, that the phase III trials confirm that chronotherapy is worth pursuing and that oncologists are willing to set personality conflicts aside and give it a try. Chronotherapy would still face a major – possibly disqualifying hurdle: logistics.

Currently, most chemotherapy is delivered to patients in big rooms with several people being monitored at a time by a hand full of nurses. Patients make their own appointments during business hours and come in to receive their prescribed treatment, often sitting for several hours while their medication drips into their veins. The

chemotherapy center must employ nurses to hook up IV's and monitor the patients, and at least one doctor who can step in to manage any dangerous side effects.

In any given state, there are up to 130 thousand cancer patients in need of treatment. Restructuring the way they receive care is no small endeavor; and giving chemotherapy accordance with circadian timing would require some major changes. First, nurses and doctors would need to be staffed 24-hours a day. While all humans have similar circadian rhythms, the best time to give a medication varies from dug to drug. Some should be given in the middle of the night, others first thing in the morning. For small hospitals and doctor's offices this just isn't feasible. Second, there could be significant problems with scheduling the delivery of medications for specific diseases. For example, if a particular clinic saw a lot of ovarian cancer patients, they would all need to receive their drugs at the same times of day. The nurses would be overwhelmed and the waiting room would be jammed with women all trying to get their medication as close to the recommended time as possible. "Do you know what my secretary would say if I told her we had to schedule patients that way?!" one oncologist exclaimed.

For these reasons, most of the clinical trials have been conducted in large teaching hospitals where nurses, residents and interns are available at all hours of the night. But sometimes even these facilities meet resistance. Shortages have led nurses to become hugely over worked at almost every hospital in America, and some are understandably unwilling to adjust their schedules to accommodate more complex drug regimens.

Beverly Teicher, who worked for the Dana Farber Cancer Research Center before taking the post at Genzyme, remembered a study that was to be conducted at Dana-Farber to look at giving certain anti-cancer drugs at different times of day. Once the study was designed and brought to the medical staff, it was the nurses who refused to participate in the trial. They claimed that this study couldn't be done because nurses only administered medications at set times during their shift. And with that, the trial was killed. This experience left Teicher pessimistic about the use of chronotherapy in mainstream oncology. "It will never make it out into the community because physicians don't have the wherewithal to deliver drugs in that way."

Patricia Wood shares Teicher's concerns. "The only way we can do this (chronotherapy) is independent of hospital staff." Wood believes that the solution is to look at automated drug delivery systems—pumps that can be digitally programmed to deliver drugs at any time of the day. These devices are already used in hospitals to deliver pain medications. Wood hopes that portable versions of the pump, already used for some chemotherapy regimens, will make chronotherapy more feasible.

The programmable pumps are about the size of a paperback novel. When loaded with a drug, the pump can be set to deliver the medicine at different rates over several hours, or to start giving the drug at a specified time. Once it has been filled and programmed at the doctor's office the patient can strap the pump over their shoulder and head home. But using these pumps for chemotherapy would require a kind of permanent IV tube to be placed in one of the patient's veins. The most common solution is to surgically implant something called a Portacath.

Patty Alessio pulls down the neckline of her t-shirt, exposing a scar about the size of a quarter just below her collarbone. One could have mistaken it for a small pox vaccination, except for the placement. The scar seems out of character for this woman, sitting in a matching sweat suit at the head of a large cherry wood dining table. Everything about her home speaks to a woman in control, from the fresh floral arrangements to the china with matching napkins she uses to serve lunch. But this spot of pocked skin is splotchy and uneven. It is a remnant of her chemotherapy treatment.

A surgeon slid a guide needle through that very spot until it reached a large vein near Patty's heart. Over the guide needle, the surgeon fed about six inches of plastic tubing into the vein. To the end of the tube protruding from Patty's chest he connected a metal disk, about the size and shape of a soda bottle cap. The top of the cap was soft, like a pincushion. The surgeon then made a pocket in the skin below Patty's shoulder into which he stitched this device, her new Portacath. A needle could then be stuck through the skin and into the pincushion, giving instant access to the vein. For the next few months Patty would have blood drawn and medicine injected through this port. She now keeps this anomalous memento in a plastic biohazard bag, stuffed discretely into the front of a blue three ring binder.

Chemotherapy can do a lot of damage to the veins into which it is injected. The portacath streams the chemotherapy into the much thicker vein near the heart, which is better able to withstand the toxins. Unlike an IV, the Portacath can't be knocked out (without a great deal of effort). It also makes round the clock infusions relatively easy to accomplish. For these reasons, many patients like Patty have a Portacath, or similar device, implanted for the duration of their treatment. One oncology nurse at a large Los

Angeles hospital estimated that between 70 to 80 percent of the patients she treats have some version of a Portacath. But with these ports comes an additional surgery, an increased risk of infection and the rare possibility of it slipping out of place.

Oncologist Raul Mena also worries that widespread use of programmable pumps will create a further line of potential errors. He grumbled about getting calls at 4 a.m. from a patient with a malfunctioning pump. "Imagine trying to teach your grandmother how to program her VCR over the phone at 4 in the morning!" But his nurse is less concerned. While walking me through the FOLFOX regimen given for colon cancer, a therapy that already requires a programmable pump, I ask her about the device. Would an aggressive sleeper like me accidentally reprogram the machine? "No," the nurse replies, "there's just this one little button to turn the thing off. If it malfunctions, you'll have to come back in to the office so we can reset it for you. Other than that, they're pretty much fool proof."

The pumps currently in use have their limitations. Most can only support one drug, two if the drugs can be mixed in the same bag. If a patient requires more than two drugs the multiple pumps must be carried in a duffle bag—a load often too heavy for older patients. The pumps also have a limited ability to be programmed. The can be set to start giving the drug at a designated or they can be set to give the drug constantly with a peak in concentration at a certain time of day. But the pump cannot start and stop itself for multiple infusions.

While the pumps do offer the freedom to leave the doctor's office, the patient must return the next day to bring the device back. Some treatments may also require that the patient wear the pump for several days in a row. This makes simple tasks like

sleeping, showering and physical intimacy very difficult. So patients must ask themselves which is more inconvenient: being strapped to a pump 24-hours a day for 5 days or visiting the doctor's office five days in a row, but going home disentangled from any medical devices. Then again, all of cancer treatment is an inconvenience.

Since the cost of cancer care is already enormous, a very real concern for patients and doctors alike is who will pay for these pumps. The cost of renting or purchasing the equipment would initially increase the cost of the treatment. Some fear that insurance companies might not cover the pumps. But evidence is accumulating that shows eliminating the need to treat numerous side effects will actually offset the costs of the pumps.

A 2004 study published in the Italian cancer journal Tumori compared the cost of purchasing pumps for chronotherapy, renting pumps and traditional chemotherapy. It found that where one course of the FOLFOX regimen costs $445, a single course of chronotherapy costs $433 or $458 depending on if the pumps were purchased or rented, respectively. The amount chronotherapy added in cost for purchasing new equipment was eventually saved in avoiding side effects.

So Now What?

Pumps, schedule changes, financial concerns, additional surgeries… some worry that these problems might overwhelm any potential benefit of chronotherapy. "It's a long run for a short slide," says Harvard oncologist Robert Mayer. Most people, including Hrushesky, don't see chronotherapy becoming a standard practice for many, many years. But there are signs that the idea is gaining ground.

On the technological front, the medical device manufacturer Aguettant has begun marketing a device called the Melodie infusion pump—a pump that can deliver up to four drugs at a time, all on different schedules. The pumps are costly, running over $10,000 for the pump alone and another $2,500 for the computer software and connection cables, but the fact that they are being manufactured at all is a sign that some investors foresee a market for programmable drug delivery. It is step towards making chronotherapy more logistically possible. In July of 2001 the Melodie pump received FDA approval.

Support for chronotherapy also comes with the accumulation of positive evidence from different fields. In 2000, Marie-Christine Mormont of the University of Paris and her colleagues published a study showing a clear link between maintaining good rest activity/cycles (which are the same as sleep/wake cycles) and cancer survival. After following 200 patients with metastatic colorectal cancer, the researchers found that patient were five times more likely to be alive after two years if they maintained good sleep/wake rhythms. The sleep/wake cycle controls the timing of all other rhythms in the body. So, in the simplest of terms, getting a good night sleep and being active during the day keeps other rhythms cycling nicely and helps your body to better fight the cancer.

Evidence for chronotherapy is building on the molecular level as well. In 2004, a study published in the Proceedings of the National Academies of Science mapped out the specific mechanisms through which clock genes interact with a certain chemotherapy drug called CY. As biologist Carla Green notes in her review of this study, this kind of research goes beyond the vague notion that clocks somehow affect

susceptibility to these drugs. The study shows that the body's response to chemotherapy drugs is not just determined by broad circadian rhythms, but that specific clock genes dictate just how sensitive the body will be to this drug.

Research that has yet to be published also shows that clocks affect cellular function in key metabolic tissues such as fat, muscle and liver. Drawing on a personal communication with Ronald Evans, a research professor at the Salk Institute, Evans noted that the number of nuclear receptors in a cell or tissue changes over the course of a day. Nuclear receptors are specialized proteins that interact with other chemicals, including drugs, on the surface of the nucleus to signal the DNA to crank out the proteins needed for metabolism. Some of these receptors are specialized to control the processing and elimination of drugs from the body. The number of nuclear receptors present determines just how many of these chemical messages get relayed to the DNA, and thus has direct bearing on how and when the cell responds to different drugs.

Chronotherapy's supporters are also becoming savvier in how they pitch the idea. Hrushesky is planning to meet with some oncologists about which chemotherapy regimens they would most like to see developed into a chronotheraputic plan. Georg Bjarnason has been meeting with pharmaceutical companies to discuss the potential for incorporating chronotherapy into the way they test new drug compounds. Chronotherapy researchers are also starting to talk to hospitals about making chronotherapy a selling point for their cancer treatment centers.

And then there are the patients. Take Betsy, for example. Since her own battle with breast cancer, Betsy has run a support group for women battling the disease. She will fly "her ladies" across the country to doctors willing to prescribe more aggressive or

cutting edge therapies, but only after she weighs the risks. Breast cancer patients have strong tradition of advocating for new therapies. It was their demanded for an alternative to the mastectomy that spurred the development of the less disfiguring lumpectomy technique.

We sit in a Middle Eastern café in San Diego, California, ignoring the din of mindless chatter to focus on more weighty matters. Her pink sweater and easy smile belie the strong and hardened woman that she is. She expertly rattles off drug names, tumor grades and genotyping facts as she recounts the profiles of the women she looks after—she is as good as most oncologists I've talked to. She grills me with a healthy skepticism of a patient advocate: What is this chronotherapy about? What does the evidence look like?

After I answer her questions, her eyes start to light up. She asks me to send her a review about chronotherapy recently published in Nature. She's excited about even the smallest potential benefit, especially if it can be no worse than current treatment. She accepts her role as survivor and counselor among many who are less fortunate than she. Despite the many women she has seen die because of failed treatments, she remains hopeful because frankly, she says, "I'm tired of going to funerals."

Betsy's hope rests within a system that has the frustrating task of balancing patient care with financial, logistical and ideological concerns—a situation that has kept chronotherapy from having its merits proven, let alone disproved. Neither the logic of a scientific paper, nor passion of a crusader has managed to push chronotherapy forward. So for now, chronotherapy remains a concept, an idea, an argument. To become a real part of medicine's arsenal it is going to need continued confirmation as well as powerful

advocacy. But not all forces for change must come from within the medical establishment. If patients show an interest in the development of chronotherapy, hospitals, pharmaceutical companies and medical device manufacturers will start to see a potential market. Chronotherapy's rescue from the mire of unscientific objections will likely come from the patients it ultimately seeks to help.

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